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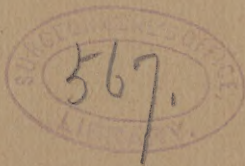
BY

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THE CONNECTION OF INTESTINAL AUTOTOXIS WITH CERTAIN COMMON FORMS OF INSANITY.*

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UNTIL quite recently the therapeutics of mental diseases have been very primitive, in view of the pathological advances that have been made in so many different directions, and do not appear to have been seriously influenced by the important researches that have marked the last decade, so far as deranged metabolism is concerned. Even to-day the management of insanity nearly everywhere consists chiefly in quelling excitement by narcotics, overcoming depression by stimulants and tonics, and affording rest, isolation, and protection.

I have for several years been impressed with the somatic origin of various psychoses, especially those which were first classified and defined by Krafft-Ebing as "acquired," and by others ascribed to certain epochs, and I have looked for some more direct and reasonable causes than those which are ordinarily alleged to exist, reach-

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ing the conclusion that in very many instances the existence of defective oxidation will explain the clinical features of numerous insanities which were formerly roughly classified with regard to their mental characteristics alone, as mania, melancholia, dementia, or still further particularized by the names which defined their periodicity, or the crisis at which they appeared, or the element of hereditary predisposition; although in a few exceptions, notably hepatic and rheumatismal insanities, the somatic element has been recognized.

The defect of most classifications of an assigned ætiology is that no serious attempt is made to satisfactorily connect the alleged cause with the symptoms and satisfactorily explain them. Granted that intrinsic defects, due to heredity, exist, no very clear or satisfactory explanation is given of what initial physical and secondary psychic disturbances follow. A great deal has been written about increased or diminished tension of the cerebral arterial system, but to those familiar with the exciting causes or pathology of insanity the irregularity of cerebral hyperæmia or anæmia must be manifest. Why a periodical mania should develop, subside, and reappear, the environment and other influences being unchanged during the entire course, has not been definitely explained. Why a confusional insanity most unexpectedly follows a surgical operation when there is little or no shock, or a form of puerperal insanity appears weeks after parturition, and when the danger of local sepsis has long disappeared, suggests the necessity of some fresh explanation.

Before going further in this direction it may be well to say that my desire for more exact knowledge in regard to the pathology and ætiology of such everyday dis-

orders as acute mania or melancholia was stimulated by the experience common to most of us, that, where psychic causes exist, not only the mental but the physical disturbance is usually entirely out of proportion to any cerebral shock or demand upon the brain, and it seems strange that where the most extreme kinds of mental strain exist in some individuals, they are attended by comparatively little or no general disturbance. I was led to reason that if subjects who are subjected to comparatively superficial mental strain rapidly develop great physical derangement, disturbances of assimilation, feebleness, and emaciation, and die in a few weeks, there must be something beneath all this—something that has been simply lighted up or induced by the preparatory condition into which, perhaps, hereditary influences entered to some extent, or not at all. The observations of Herter and Smith point to the fact that that protean neurosis, neurasthenia, is closely connected with some form of disturbed intestinal function, and Eccles and Gautier clearly recognized the insufficient activity in the oxidation processes with the presence of the products of incomplete metabolism, and with an increase of the combined sulphates in the urine. The excellent work of Bouchard, Rodriguez, Chardon, and Chevalier Lavaure, and the more recent papers in your own country of Macpherson, Eccles, St. John Bullen, and Turner, have led to the inquiry whether a large number of acute insanities are really not after all due to primal intestinal disorders, and if even the course of the chronic psychoses must not be more or less modified by the same agencies: and whether, this being true, we should not in the future direct our treatment more than we have in the past to the care of the digestive organs, placing

less reliance on the use of the conventional narcotics, or other familiar modes of treatment.

With this end in view I made many months ago a series of investigations, the results of which have been based upon experiments with animals and clinical observations conducted in the hospitals and asylums with which I have been connected, and in my own practice and elsewhere. More than fifty cases of different kinds of insanity have been observed, which include examples of acute and chronic melancholia and mania, simple delusional insanities, primal and terminal dementias, paralytic dementia, periodic, puerperal, and traumatic insanities, and the alcoholic and drug psychoses. The variation of the urine and fæces was noted, and all the cases were carefully watched. It would be impossible in a brief paper of this length to more than summarize my results, and it is my intention this evening to simply sketch the work that has been done.

The experiments were undertaken to determine first whether there was any specific or noso-toxicity of the urine of the insane; and, if so, what the nature of such toxicity was; next, to discover, if possible, how important and general was the theory of uric-acid poisoning; and again, whether mental disorders were produced and modified by an autotoxæmia; whether the offending substances were the leucomaines or the intrinsic products of putrescence in the intestines. According to Marie and Bosc, the urine of insane persons possesses a toxicity which varies and is more or less identified with the different forms of insanity. They found that it was increased in agitated melancholia, as well as in persecutory insanity and excitable mania, while there was only a normal amount in quiet mania, and the toxicity was

much reduced in purely stuporose and senile conditions. As the result of their experiments upon animals, hyperthermy and anæsthesia, auditory hyperæsthesia, diminished reflexes, psychomotor disturbances, and agitation ensued; but their conclusions, however, were doubted by Seglas and Ballet, who contended that there was nothing distinctive in the findings. For the purpose of satisfying myself as to the possible extent of noso-toxis, I selected six patients, from whom the urine was obtained weekly, and conducted a series of experiments to determine whether there was any uniformity or peculiarity, but with negative results.

Rabbits were chosen and kept closely under observation for a number of days, and, although some of them manifested rather striking nervous symptoms, as well as the hyperthermy observed by the authors referred to, the results were neither constant nor characteristic. Two of the patients whose urine was injected were melancholics, one was a case of acute mania, another of chronic mania, a fifth of paretic dementia, and the sixth of periodical insanity. The resulting effect seems to depend very much upon the increased specific gravity of the specimen, and on the evidences of intestinal disorders and malnutrition. The urine of the paretic was always exceedingly toxic, which property was possessed by that of the periodic patient, whose urine showed a large amount of indican, while in only one of the other cases of mania in which the specific gravity of the urine was high, was there any result effected by its injection. In these dense urines there was an increase of the combined sulphates and urea. Large quantities, amounting to forty cubic centimetres of the urine of the melancholic, were injected without any apparent effect, so I

was forced to abandon the idea that the excreta, in certain forms of insanity, presented specific toxic qualities. The only interesting psychic manifestation besides an apparent stupidity was the causation, in the rabbit that had received the injection of urine from the parietic patient, of rather a curious condition, which led me to believe that hallucinations of vision existed. There was absolutely nothing, however, that could be regarded as uniform, although frequent injections were made. So far as the influence of uric poisoning is concerned, I am clearly of the opinion that it has not as much to do with the genesis of mental disease as is alleged for it by the more enthusiastic, but in those cases in which it is supposed to play an ætiological part it is a very grave question whether its presence is not indicative of another kind of poisoning, which is the result of the destructive metabolism of nuclein, the amount of uric acid measuring the amount of leucocyte activity, and we are confronted with the query whether the initial destruction is not due after all to a primary intestinal disorder. The symptoms produced by the injection of urea and uric acid into animals, as detailed by Bouchard, though possessing a certain uniformity, have too limited significance in view of the varying symptoms which enter into the clinical picture of various insanities due to the absorption of putrescent substances. One distinguished writer has announced that melancholia especially is due to the accumulation of the second of these substances, and that one of its important features is the increased arterial tension, an assumption which I do not think is always tenable, though it may occasionally exist, for my own experience teaches me that there are many cases of this mental disease

where the arterial condition is the reverse. So far as the influence of retained leucomaines is concerned, there seems to be much more reason to believe that, in the subjects where there is the retention of the physiological products of waste, disorders of the nervous system generally ensue. Salomon has found that when paraxanthin was introduced into the blood stream of the smaller animals, states were induced resembling some of the psychoses observed in man, and I am informed that he has produced in a mouse a condition, so far as objective appearances are concerned, closely resembling stuporous melancholia. His experiments in 1892, and those of Mendel subsequently, prove that it was possible to produce symptoms similar to those of katatonia by the injection of this substance into white mice, dogs, and cats. Vaughan injected a small quantity of hypoxanthin into a frog, which some hours afterward became convulsed. Remembering that paraxanthin and heteraxanthin are the organic analogues of the vegetable alkaloids caffeine and theobromine—one being a dimethylxanthine and the other a methylxanthine—the natural speculation may arise whether the effect upon the nervous system of the latter might not be duplicated in the organic extracts, although Vaughan and others have concluded that the organic alkaloids obtained from ptomaines, or rather diamines, have not the identical physiological effects of such vegetable alkaloids as atropine, morphine, coniine, etc.

At my request, Dr. E. E. Smith, of New York, prepared a quantity of hypoxanthin in the following manner:

Liebig's extract of beef was dissolved in a large volume of water, and lead acetate added till no further pre-

cipitate was produced; the solution was filtered, the filtrate treated with hydrogen sulphide till the lead was precipitated, and this filtrate evaporated to a small volume and the creatine crystallized in the cold. The evaporation of the crystals was aided by the subsequent addition of several volumes of an eighty-eight-per-cent. alcohol. The mother liquor, after removal of the alcohol, was precipitated with ammonia and silver nitrate, the precipitate dissolved in nitric acid of specific gravity 1.1 by the aid of heat, and the solution cooled, when crystals of hypoxanthin silver nitrate separated out. This salt was suspended in water, decomposed with hydrogen sulphide, and the filtrate evaporated to a small volume, whereupon hypoxanthine nitrate crystallized out.

Microscopical examination of the crystals of hypoxanthine nitrate showed the characteristic form with the exception only of one or two acicular crystals, doubtless mere traces of adenin.

With this product I conducted a series of experiments on rabbits and monkeys. Hypoxanthine was mixed with the food and given in doses varying from ten to fifteen centigrammes at intervals of an hour, until a hundred and fifty centigrammes were given, without any satisfactory results so far as the production of symptoms of any kind was concerned. Of four rabbits, only one presented toxic symptoms, and to a Java monkey as much as fifty centigrammes were given without any apparent effect. The susceptible subject was a lively nervous rabbit weighing three pounds and a half, to whom twenty centigrammes were given in bran. Within five minutes after taking it, the animal manifested some excitement, rubbed its paws vigorously, and

was restless and disturbed by noise or jarring of the floor; its ears became exceedingly congested and its reflexes were affected by the slightest tap. This irritability gradually subsided, so that at the end of two hours it became dull and stupid, and did not resist pinching or other forms of stimuli. Its paws could be pricked with impunity and without any apparent evidence of feeling. Its pupils were widely dilated, and the pupillary reflex was lost, while there seemed to be retinal insensibility, for it did not mind a lighted match or the application of an irritant. When with much urging it was made to move, it dragged its hind legs, and there was no effort to escape. It remained in a condition of torpor for over an hour and gradually resumed its normal condition of liveliness. The same rabbit subsequently manifested identical phenomena when twenty cubic centigrammes of a fifty-per-cent. solution were introduced into the circulation.

It would appear that the intestinal toxalbumins have more to do with the production of disturbance of the nervous system than the leucomaines, which undeniably have an effect, though not a very marked one. Selmi obtained ptomaines from the urine of a parietic patient which, when injected into an animal, produced convulsions, and according to Vaughan and others most of the ptomaines produce convulsions and other forms of hyperkinesis.

A study of the cases that have formed the basis of observation for the past year unquestionably bears out the assumption that disturbances of the gastro-intestinal tract, more often than is generally supposed, are attended by bacterial necrosis and the introduction into the general circulation of certain very virulent toxic agents

whose effects are expended mainly upon the nervous system. I think I am safe in saying that nearly all the rapidly developing confusional insanities have this explanation, and we must, therefore, be on the alert for such a cause, even when the case has commonplace features. No other alternative has presented itself so strongly to my mind as that of intestinal putrefaction, and in all the patients whose urine was examined a decided increase in the amount of indican was found, even when the diet was carefully regulated.

A sudden and rapid development of incoherence, then, with malassimilation, highly colored urine, and delusions that are unsystematized, clearly suggests an inquiry into the condition of the organs of digestion, and the first step should consist in a complete examination of the urine and fæces. Even in the chronic insanities the occurrence of *accès* and convulsions has, in my experience, been attended with some defect of metabolism, and the determination of the sulphate ratio has afforded me great help in diagnosis.

Turner, in an admirable paper, determined that the ratio of the preformed and aromatic sulphates in general paresis, while not very markedly increased in the early stages, became decidedly so in the established disease or coincidently with the *accès*, the ratio rising and afterward subsiding.

It would appear, from my own cases, that those usually showing little or no excess of combined sulphates include examples of chronic delusional insanity, chronic melancholia, and some of dementia. In individuals whose mental condition was one where imperative concepts played the chief part, the urine showed nothing that was unusual, at least so far as

absorption of intestinal putrefactive products was concerned.

From the data obtained from all available sources, my own cases and others, it would appear not only that the ratio of the sulphates between themselves and to the urea, and the presence of indican in considerable amount, are indications of intestinal putrefaction, which no doubt influence the course of various insanities, but that a large increase of the combined sulphates has much to do with the genesis of various psychoses, and Bence Jones has noted this in delirium, while Regis and Chevalier Lavaure recognize the gravity of septic poisoning in other well-known mental conditions, but so far, though our knowledge is somewhat crystallized, the matter is still unsettled, and there is much to be learned with regard to the importance of the sulphatic ratio. My investigations convince me that the presence of indican in the urine of the insane has the most significance, so far as constancy is concerned, for in nearly all the cases which were not simply evolutional it has been discovered in excessive quantities, in connection with the development or as a feature of an exacerbation of an existing mental disorder.

What is an excessive quantity? may be asked. The reply is: Any amount that can be detected in the urine by Jaffe's test, even if a weak reaction is obtained. Smith fixes the harmful amount at anything more than five milligrammes in twenty-four hours, and the color may vary from a light pink to a deep purple. In two or three of my cases the appearance of indican was nearly always coincident with the outbreak of new symptoms or the intensification of old ones, and it always marked the existence of a putrefactive process, bearing out the axiom

that the presence of indol indicates bacterial death in the intestines. As regards the special connection of urinary findings of this kind with different kinds of mental disease, it would appear that in all forms with loss of weight and depression the sulphate ratio between the combined and preformed sulphates was lower than in health. It has been pointed out by Senator that an abundant appearance of indican under these circumstances indicates starvation, and, from the lowered quantity of preformed sulphates found in cases of inanition, Herter and Smith agree with him. In melancholia especially, the amount of indican depends upon whether the disease is of the stuporous or agitated variety, the quantity of this substance found not being so great in the former. In one of the series of cases in Bloomingdale Asylum, examined by Dr. Dodd, it was absent only once in a series of seventeen examinations, and always existed in large quantity with a corresponding decrease in the sulphate ratio, the latter varying from one half to one twelfth. In such cases of melancholia the blood-corpuscles and hæmoglobin seem to undergo a decided diminution, which has been observed in other conditions where anæmia existed in association with the increase of the combined sulphates and the presence of large quantities of indigo blue. I believe it was the late Sir Andrew Clarke who first pointed out the connection between anæmia and the absorption of the products of intestinal putrefaction. In all the melancholic and other patients in which the coincidence existed, the variations in the hæmoglobin and red corpuscles were closely connected with the absorption of toxic substances, the extent of which was announced by the increase of the combined sulphates,

while the physical appearances were those of malnutrition. Such a case was that of a young lady whose feebleness and exhaustion were extreme, and were coincident with a mental condition manifested by an initial neurasthenia, with digestive disorders, depressing delusions, self-accusation, and attempted suicide. The hæmoglobin was reduced to thirty per cent., and the red corpuscles to less than three hundred thousand. This state existed in connection with a low sulphate ratio and a constant output of indican, notwithstanding the fact that appropriate diet was ordered. The course of treatment, in which nuclein-forming agents and lavage and intestinal washing figured, cured her in two weeks, after arsenic and iron and forced feeding had failed.

Some forms of melancholia are undoubtedly due to autotoxis dependent upon impaction and copræmia, although the passage of an apparently sufficient amount of fæcal matter may incline the observer to ignore the existence of constipation as a cause. If the urine of such patients is examined, a large excess of aromatic sulphates will be found, with increased indigo blue and possibly skatol. Two such cases have made a great impression upon me, for the reason that, notwithstanding the passage of what looked like fair-sized stools, which to all appearance contained the recognized *débris* of food taken within twenty-four hours, such was not the case, and a certain accumulation existed which gave rise to a melancholia of an almost stuporous kind at first, but which subsequently became excited after a week or two, and was quickly cured by the recognition of the obstruction and its removal. In this case the increase of ethereal sulphates was enormous, the pres-

ence of indican being detected in large quantities. After the bowels were emptied and naphthalin was given, the delusions, which were more or less systematized, quickly disappeared, and the urine became normal. It would seem that circumstances sometimes modify the course of a chronic melancholia by favoring the increased elimination of more or less toxic products, so that an improvement in the mental state is witnessed, at least for a time. In a case reported by Eccles, an attack of influenza in a melancholic caused an increase in the elimination of urea and the leucomaines, with a coincident improvement of the mental depression, which, however, reappeared when the pyrexia subsided.

By far the most suggestive cases in which autotoxis from intestinal disorder plays a part are those of acute excitement, especially where there is rapidly developing incoherence and confusion. These, in my experience, have, as a rule, been associated with corresponding evidences of intestinal disorder such as have been described. Lively and generally fleeting illusions and hallucinations and delusions developing after insomnia, loss of appetite, and constipation, the delusions being unsystematized, are features, and if such derangement be connected with urinary findings of the character I have mentioned, and the clinical evidences of physical disturbance, I think the intestinal disturbance may be always looked upon as a cause.

The more sudden and active are the manifestations when unsystematized delusions or hallucinations are expressed, the more positive are, in my experience, the indications of autotoxis. So characteristic, for instance, are the loquaciousness and incoherence that Jacobson, who has described the toxic insanity of nephritis, has

applied the name of "*Verwirrheit*" to the confusion, which is almost allied to delirium. Acute hallucinatory insanity is often expressed by pseudaphasic confusion, and is often undoubtedly due to the cause I have mentioned, and there are even cases of extreme neurasthenia in which consciousness is more or less affected, and where there is no special delusional system. Occasional remissions of some duration are possible in these forms of general derangement, during which the patient recognizes his false ideas and speaks of them. In some of these cases pseudaphasic confusion is expressed as the result of misleading auditory hallucinations which the patient is unable to correct. To the excited psychoses belong certain short-lived varieties of mental disturbance of this kind attributed to shock, and denominated traumatic insanity, in which such confusion is a characteristic. To this class belongs a case recently seen by me in consultation with Dr. Lusk, of New York.

The patient was a woman, thirty-seven years of age, who went into St. Vincent's Hospital on January 28, 1896. She had had some irregular menstruation with slight uterine hæmorrhages between the menstrual periods, and once or twice in her life had had epileptic convulsions. The condition of the heart and lungs was negative. Abdominal and vaginal examination revealed the presence of a fibrous tumor, which was removed by operation on January 29th, on that day the temperature being normal and the pulse 90, but the urine had a specific gravity of 1.035, and contained abundant urates.

After the operation no untoward results occurred until the next day, when there were restlessness, insomnia, flatulence, and a slight rise of temperature, which

continued, so that on the evening of the 31st it had reached 103° . She was troubled with abdominal discomfort, eructations of gas, and increased nervousness. The bowels moved for the first time on February 1st, the amount of faeces being very small; on the 2d the enema brought away a large movement. She became flighty on the evening of the 2d, and had delusions and terrifying hallucinations of a persecutory nature; the temperature meanwhile varied between 101.2° and 102° , with broken and uneasy sleep procured only by morphine and chloral.

The urine was now superficially examined, showing an abundance of urates with high specific gravity (1.025), no albumin, and sugar. Her incoherence almost amounted to delirium, and she cried, and was excited and anxious to leave her bed. For several days there was no particular rise of temperature, there being no greater advance than 102.8° , with a corresponding rapidity of pulse. The intestinal disturbance still continued, and was very general. She did not recognize persons, but called them by wrong and fanciful names, and had no idea where she was. She had been fed with nutritive enemata and milk, and on the 14th a critical examination of the urine was made at my suggestion, which disclosed the following appearances:

A moderately large amount of indican and a lowered ratio of preformed and combined sulphates; the combined sulphates measured by the Salkowski-Baumann method being 0.25 gramme, and the preformed sulphates 0.45 gramme in the urine of twenty-four hours, while the urea was reduced to 11.81 grammes in the same period.

The ratio of uric acid and urea was 1 to 38.

Naphthalin was suggested and given in doses of four grains every two hours, being preceded by calomel and soda. Her condition, which had up to this time been almost continuously one of incoherence, promptly cleared up, and she but occasionally expressed delusions. The next day the temperature fell to 98.8°, and remained normal thereafter. She recognized that she had been irrational, and after the 23d there was little mental disturbance left, the specific gravity of the urine falling and showing a rapid decrease in all abnormal constituents, while her stools, which had been of a clay color, were well formed and regular. The sulphate ratio became normal, and the total sulphates were properly proportionate to the urea; the ratio of uric acid to urea was 1 to 50.

Another case in which the condition of the urine bore a very close relation to the variation of the mental symptoms was that of a young married lady, who upon two previous occasions, one far apart from the other, had manifested symptoms of an alternating character, there being usually an initial melancholia and succeeding light mania, which increased and had to be controlled by morphine and hyoseyamine. Her periods of mental derangement generally extended over several months, and seemed to bear close connection with a more or less profound disturbance of digestion, and were distinctly modified by the menstrual periods. The attacks of 1893 and 1894 were managed in the ordinary way, and there was a general amelioration of the symptoms and final subsidence, the convalescence occurring after removal from home. In 1895, after a protracted neurasthenia, she was affected with a maniacal condition marked by very great muscular violence, incoherence,

and lively delusions, some of which were erotic and unsystematized. So extreme was her condition as to need the services of three nurses, and, despite their uninterrupted care, she became filthy and destructive, tearing her clothes, breaking such objects as she could lay her hands upon, and requiring dangerous quantities of hyoscine for the production of quiet. Her condition was exceedingly variable, and when she was not engaged in impulsively destroying things about her and assaulting her nurses, she scribbled and wrote incessantly, and there was almost constant verbigeration. Her bodily condition was one which gave me a great deal of worry, for she rapidly lost flesh, and this despite the fact that large quantities of food of a condensed and apparently suitable kind were taken.

Repeated examinations of the urine and the fæces showed a very decided disturbance of gastric and intestinal digestion, and her symptoms kept pace with the variations in these processes. Her mental state, which was most irregular and apparently uninfluenced by anything in her surroundings, revealed an interesting condition of affairs, which was so constant and consistent as to convince me that the insanity was kept up by the absorption of some toxic material. Her periods of excitement and confusion were always attended by a reduction in the amount of urine excreted, by an increase in the ratio of preformed and aromatic sulphates and indican, and by the presence of those signs of impaired digestion which indicated an intestinal putrefactive process. Certain psychical prodromes of attacks after periods of comparative lucidity were nearly always immediately connected with the presence of an increased sulphate ratio. At one time, before this connection was realized,

the prognosis was exceedingly bad, because of the extraordinary condition of physical exhaustion.

This patient had received up to this time nearly all the approved restorative agents and tissue builders that were available, and one twelfth of a grain of the hydrobromide of hyoscine daily. When this point was reached, the diet was restricted, nitrogenous substances being excluded as far as possible, and thorough intestinal disinfection was obtained by means of charcoal, salicylic acid, and the carbonate of guaiacol, the patient meanwhile being given large draughts of water, and her lower bowels flushed by the long rectal tube, with a mild solution of boric acid. At regular intervals she took calomel purges, and a preparation of the red marrow of the small bones of the calf, to which reference will presently be made. The good result was almost immediate. Excitement subsided, and there was a rapid return of self-control, with the disappearance of the delusions, and a general subsidence of all mental disturbance. Continued and sufficient sleep was obtained for the first time in months, and the patient rapidly recovered. Within a few days after the intestinal antiseptics had been established, the urinary condition became apparently normal, the ratio of sulphates resuming its normal standard, and the specific gravity of the urine was promptly lowered, while the indican disappeared. A distinct and decided gain in color and flesh was inaugurated, and in three weeks after treatment the red blood-corpuscles had increased fifty per cent., while the percentage of hæmoglobin, as measured by the Reichert instrument, rose to 105.

The causation of puerperal fever by the death of the *Bacterium coli* has been demonstrated by Budin, who

has studied the febrile disturbance in connection with fæcal accumulation. Undoubtedly, many puerperal insanities have some such explanation as this, especially those of the maniacal variety, which often develop in a very few days after parturition. A case I have recently seen was one in which there was absolutely no ascertainable local infection and in which there was no unusual rise of temperature, and a rapid recovery took place after the establishment of intestinal antisepsis.

Alcoholic insanity, as well as other forms, where acute or chronic variations prevail, must, I am convinced, be studied with regard to the conditions of the intestines, and it does not do to ascribe its origin altogether to general exhaustion or to circulatory changes, or to the well-known effects of alcohol upon the nervous tissue, although undoubtedly all these conditions exist at some time or other, and in different cases play a part. If we stop a moment to consider the clinical features of acute alcoholic insanity, we shall find many of the symptoms of a rapidly developing toxæmia, quite apart from that effect upon the nervous system which may be produced by the agent itself. The cerebral hyperæsthesia, rapid changes in perverted perception, the development of the peculiar hallucinations in which rotten substances, worms, bad odors, or other horrors appear, often figure; the hyperkinesis, cephalalgia, malaise, etc., and the antecedent history of gastric intestinal disorders, the presence of abundant aromatic sulphates, urea and indican in the urine, and possibly skatol, the foul small stools or diarrhœa, the final unstable and changing delusions, exhaustion and death, are suggestive. When we consider that the proteids have passed undigested through the small intestines, and have accumulated below, where

they lie enfolded in a congested and feeble gut, it is not difficult to appreciate the fact that they form a rich field for bacterial attack, with the resultant introduction into the system of an amount of toxic material sufficient to produce a most serious change in the functions of the brain and cord. The alcoholic extracts of fæcal matter, according to Bouchard, are far more toxic than ordinary putrid matter, so it will be appreciated how readily skatol, indol, and other alkaloids of the fæces may be introduced in such quantities as to do much mischief. The successful treatment of the cases of alcoholic insanity that have come under my notice certainly goes far to strengthen this view.

The insanity developing after very acute diseases, especially influenza, is probably primarily dependent upon the intestinal congestion and derangement of the mucous membrane, which is a part of the general disorder elsewhere, but in typhoid fever, where specific intestinal regions are attacked, it does not appear that there is any undue appearance of indol in the urine, although the appearance of post-febrile insanity in this disease would make this seem impossible, at least in a small number of cases.

The practical management of these cases not only includes the provision of an absolutely suitable diet, but the use of antiseptics, and recourse to mechanical means for the purpose of cleansing the gastric tract. That the lower bowel is the seat of infection appears to be very well established by the experiments of Baumann, who found that when a fistula was made in the portion which included the lower portion of the small intestine, there was a disappearance of the indol, phenol, and the other ethereal sulphates from the urine, but that

when the intestinal contents were allowed to pass through the lower natural outlet, the putrefactive products were largely increased and their presence was again detected in this fluid. This discovery shows the necessity for thoroughly washing out the lower bowel from as high a point as possible, and a long rectal tube should always be used for this purpose.

Macpherson's plan, tried with some success, is based on a recognition of the fact that when the antiseptic power of the acid of the gastric juice is impaired, there is an indication for the use of intestinal antiseptics with primary recourse to hydrochloric acid. Macpherson resorted first to lavage, which was followed by a dose of calomel at night, a saline purge in the morning, and the subsequent administration of naphthalin in doses, at first of thirty grains daily, which were increased to eighty grains.

In my selected cases I used a variety of intestinal antiseptics, the list including naphthalin, salol, and the carbonate of guaiacol, charcoal, borax, and the salicylate of sodium. Several cases were put upon small repeated doses of calomel. These drugs were faithfully tried, and although with naphthalin I sometimes obtained excellent results, and in one case of traumatic insanity very prompt ones, I found that upon several occasions it gave rise to diarrhœa, great muscular weakness, and twice strangury, and the urine was colored with hydroquinone.

The administration of phenol or its derivatives may, under some circumstances, mask the results of urinary examination, as was the case in a recent experience. The patient had submitted himself to treatment by a physician for a supposed tuberculous affection, receiving injections of a preparation which contained phenol and

pilocarpine. A few days after treatment he became wildly insane and attempted suicide. An examination revealed an entire absence of the preformed sulphates and indican, but a very large amount of combined sulphates. In this case the phenol entirely changed the urinary findings, as it always does. There was no intestinal disorder or there would have been indican, and the conclusion was reached that all the mental derangement was due to the pilocarpine.

Salol was unreliable and of slight service, and was often passed in an unchanged condition in the fæces.

Even with this drug administered in large quantities, it was apt to be found in small round balls in the fæces, and it is therefore recommended that all intestinal antiseptics should be given in small and repeated doses.

Naphthalin, if administered in capsules, which, as a rule, is necessary because of its offensive odor, is sometimes passed in an unaltered state. My experience is that of Herter and Smith, that there is no agent which approaches salicylate of sodium, so far as its antiseptic advantages are concerned, and I have given it in from ten to fifteen grains, thrice daily, and found it of especial value in melancholia and other insanities where the cerebral condition is one of anæmia. The use of this drug, which produces a condition of increased arterial tension, is rather against the theory that uric acid produces cerebral symptoms, for not only is it of service because of its antiseptic action, but in the anæmic brain of melancholia it certainly brings about an improvement through accession of new blood and nutritive material.

In insanity of a toxic nature there is, as we know, a destruction of hæmoglobin, and a very greatly reduced number of red corpuscles. This condition of affairs is

not only met with in the acute insanities due to the absorption of putrefactive products of intestinal indigestion, but in old insanities as well, and Johnson-Smyth found the red corpuscles reduced to 4,070,000 and the hæmoglobin to fifty per cent. in the case of secondary dementia.

So far as the nutrition of the individual is concerned, I have had the best results with a combination which is a rapid producer of nuclein, and when we appreciate the fact that in the majority of these cases there is a destruction of the coloring matter, as well as other blood elements, the provision of some agent rich in this substance is an absolute necessity.

Remedial measures of this kind consisted in the use of a combination of a glyceride of the red marrow of small bones with bullock's blood, the amount of glycerin being regulated both in quantity and temperature so that coagulation does not take place during its preparation. With this preparation I have been enabled to prevent waste, and build up my patients much more rapidly than with any of the other more popular restorative agents, and its use at two of the large hospitals for the insane in New York was attended by an increase of red corpuscles to the extent of fifty per cent., and depressed states were quickly helped.*

The possible conclusions are, I think, the following:

1. Urines rich in indican contain very little or no preformed sulphuric acid, and are toxic.
2. When the sulphate ratio is materially changed, it

* The preparation which has been called carnogen by its manufacturers was that used in the Hudson River State Hospital in Poughkeepsie. See Dr. Pilgrim's article in the *American Medico-surgical Bulletin* for June 6, 1896.

is likely to indicate autotoxis in connection with an increase in the amount of combined or ethereal sulphates.

3. Such indications are generally found with acute insanities, in which rapidly developing symptoms occur.

4. Fugacious and changing illusions and hallucinations, unsystematized delusions, confusion and verbi-geration in connection with insomnia, pallor, intestinal indigestion, constipation, and rapid exhaustion are due to autotoxis.

5. Paranoiac states, or those in which concepts are the features, chronic stuporous conditions, and certain forms of dementia have little to do with the formation of intestinal products of putrefaction.

6. Various post-febrile, traumatic, alcoholic, or drug insanities are those in which autotoxis is most constant.

7. The variations in the excretion of combined sulphates keep pace with the changes in the progress of an established insanity, *accès* and epileptoid attacks being directly connected with putrefactive processes.

8. The most successful treatment consists in lavage, intestinal douches, gastric and intestinal antiseptis by means of hydrochloric acid, borax, salicylate of sodium, charcoal, guaiacol, or naphthalin in small repeated doses. The administration of a combination of the red marrow from the small bones, blood, and glycerin.

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Discussion.

The PRESIDENT congratulated the society upon the presence of so distinguished an authority as the author, a courtesy which he hoped would be reciprocated by the reading of a paper by an Englishman before the Academy of Medicine of New York at some future date. He recalled the excellent work done by the author during the last twenty years in the department of medicine with which he himself was most associated. The paper opened out new and original ground, though he supposed the author himself would admit that much

of it was speculative. Many of his conclusions, indeed, could not at present be implicitly received and accepted, and autotoxis would not drive out of the field all the older methods of dealing with this class of cases, though it might prove a valuable help in treatment. He recalled the fact that Dr. Lauder Brunton had pointed out the resemblance which exists between the languor associated with indigestion and the effects of curare poisoning, and that he had suggested that these symptoms might be due to the absorption of poisonous matter from the intestines, probably of the nature of ptomaines. It was only necessary to suppose an excessive production of these ptomaines or their imperfect destruction by the liver, which, under ordinary circumstances, prevented them reaching the circulation, to understand that this failure to protect might have far-reaching consequences. They had only to imagine this to see that in the long run a condition might be engendered which might culminate in melancholia with stupor, evidently strictly analogous to the autotoxis to which the author had invited their attention. That the production of these bodies in the intestine might be enormously increased in certain states had been clearly demonstrated, and he himself was inclined to believe that their presence in excess in cases of intestinal catarrh might readily give rise to the mental consequences associated with this condition. He pointed out that there was a well-known type of hypochondriacal melancholia associated with catarrh of the transverse and ascending colon in which the mental characteristics were out of proportion with the lesions, cases in which there was no family history, and the symptoms yielded readily to a visit to Carlsbad or Marienbad. He had often thought that the symptoms in these cases might be due to excessive production of ptomaines in the intestine or to their imperfect destruction by the diseased liver. The possibility of putrefactive changes in the intestine and the consequent production of ptomaines were, of course, very great and very varied. He mentioned that, according to Mr. J. Murray, of the

British Museum, there were 128 genera of microbes and 169 fungi which thrived and flourished in faecal matter; many of them were peculiar to particular kinds of faeces, 45 to the horse, 35 to the dog, 28 were peculiar to birds, and 21 to the faeces of man. It was clear, therefore, that faeces afforded a very favorable and congenial nidus for fungoid and bacterial growth, and any change in the physical contents of the lower bowel or any change in their environment interfering with the fungoid struggle for existence, by giving advantage to one variety, might allow of the production of an excessive amount of certain poisons, followed by symptoms of poisoning. He asked whether the brain itself might not provide poisons, seeing that poisonous ptomaines had been proved to develop in cerebral matter after death, and it was possible that under certain conditions of malnutrition similar products might be produced at an earlier period. Muscles were known to develop various alkaloids during life which might, under particular circumstances, even determine a fatal effect. It was also worthy of consideration whether the epileptiform seizures which checkered the course of the later stages of general paralysis might not be due to autotoxis. There was a gradual degradation of nutrition and possibly incipient decomposition of albuminous tissues which might produce substances acting as poisons on the nerve cells, producing a special train of symptoms along with a rise of temperature. Selbing had shown that ptomaline was found in the general paralytic and in pneumonia, and one was familiar with the fact that washing out of the lower bowel was often the means of arresting the epileptiform attacks which characterized the later stages of general paralysis. He supposed the author would admit that the subject was at present better fitted for the laboratory than for academical discussion. His title, indeed, was very comprehensive, for it might be made to include all forms of moral and intellectual auto-intoxication, a phenomenon which resulted from undue egotism and the concentration of the energies on selfish or de-

grading objects. Ideal microbes and emotional ptomaines would lead them too far afield, and he would, therefore, not enter upon their discussion.

Dr. HAIG said it was now nearly eight years since he had first called attention to the presence of an excess of uric acid in the urine of cases of mental depression and of epileptic convulsions, etc., and he was still of the opinion that the symptoms in such diseases, now referred by some to intestinal putrefaction, were really due to the presence of an excess of uric acid in the blood. The uric acid altered the circulation throughout the whole body; the altered circulation in the brain accounted for the mental symptoms, and that in the stomach and intestines caused putrefaction to take the place of digestion. He had been much interested in what the author had said about the beneficial effects obtained by the use of calomel, because calomel cleared the blood of uric acid. It would, therefore, tend to prevent the modification of the intestinal circulation, which was the cause of the putrefaction. Salicylate of sodium also cleared the blood of uric acid and so prevented its exerting its usual effects. In one of the cases on which the author had laid considerable stress, he noticed that the patient got better when the regimen was changed, but they had not only changed the diet but given antiseptics and washed out the intestines as well. He had laid great stress upon these things but had said little about the diet. His own idea was that they gave far too much nitrogenous food, and when this was discontinued and the introduction of uric acid put a stop to, the patient got well. Many patients suffering from mental disease had been cured simply by diet, without any attention being paid to intestinal putrefaction. The points about uric acid which he wished specially to bring to the notice of those interested in mental diseases were the well-marked clinical signs of its excess in the blood—viz., high blood pressure and scanty urine. In some of the author's cases he had noticed scanty urine, and this, no doubt, meant an abundance of uric acid in the blood.

If they controlled that either by diet or by drugs they would control the circulation and the mental disease.

Dr. ANDRIEZEN said there was no doubt that one source of the poisons which generated insanity was inside the body during life (poisons of endogenous origin). From bacteriological study we knew that actual toxins could be obtained from the cultures of various pathogenic bacilli—such as those of cholera, typhoid, tetanus, etc., which, injected into the body of man or animals, produced the special and characteristic phenomena of the disease in question (Koch, Pouchet, Brieger, and others' researches). Referring to the intestinal poisons arising from constipation, it was well known that in those accustomed to a *daily* evacuation of their bowels a comparative slight delay (a few hours to one day) was sufficient to bring about headache and depression of spirits, which immediately passed off when the bowels were relieved. The mere retention of faecal matter, even for a few hours, permitted of the passage of a certain quantity of poison into the blood. He found it difficult to explain this circumstance on the hypothesis of uric-acid formation. An excess of uric acid would doubtless also give rise to much the same effects, but the rapidity with which the effects followed mere faecal retention showed that the source of the symptoms must be referred to the intestines. It was very important also to bear in mind what Dr. Lauder Brunton had shown—viz., that a great amount of toxic matter might be produced from disorder of the stomach, as in various gastric catarrhs. Dr. Andriezen mentioned certain cases of hysteria with dilated stomach, in which washing out the stomach and giving small doses of naphthalin (five grains) had brought about a very prompt recovery. Of course, other cases of hysteria, those with a different pathogenesis, did not react to this kind of treatment. In the cases of hypochondriacal melancholia without neurotic taint or history he could bear out what the President had stated, and he believed that these belonged to much the same category as the hysteria noted above,

only the changes were more extensive and severe, and the mental symptoms correspondingly increased. Toxic absorption from the gastro-intestinal tract, with or without morbid changes in the portal blood, could produce chloroses and anemias of various degrees, and in some cases of pernicious anemia such poisons (different diamines) had been found in the feces by Hunter. The sluggish movements in the gastro-intestinal tract and its lowered vitality in melancholia favored the development of ptomaine-producing micro-organisms. Such cases showed an increase of the aromatic sulphates in the urine—a good index of the amount of intestinal putrefaction going on. In epilepsy and in general paralysis the accumulation of such toxins in the blood favored and brought on convulsive attacks. The tendency of chronic Bright's disease to intensify existing symptoms of toxæmia and even to favor acute convulsions (*i. e.*, poisoning of the cerebral centres), as in pregnant women, was pointed out, and the importance of it in the clinical course of certain insanities emphasized. He was unable to agree entirely with Dr. Hamilton, that nearly all the rapidly developing manias and insanities, with hallucinations or acute mental confusion, were of autotoxic origin. In many such cases quite other and adequate causes could be easily ascertained; though errors of diet and digestion, neglect of the bowels, and consequent auto-intoxication from the intestines, might play a minor part. He was chiefly impressed with the frequency with which such autotoxis might occur, and thus aggravate the symptoms in *already established* insanities, such as general paralytic, epileptic, alcoholic, and slowly developing delusional insanity. The clinical phenomena in these cases were a slight subacute delirium with restlessness, the patient stumbling and fumbling about in his room, with insomnia, which did not react to the usual sedatives and hypnotics, and where the temperature was slightly raised, the tongue furred, the breath offensive, and the skin and flesh peculiarly liable to undue markings like bruising, even from mere rest-

lessness and the pressure of garments alone. Where he had examined the urines in such cases (about nine or ten cases) he had noticed considerable excess of indican, as compared with the same case after such a delirious episode in the course of the insanity was over. Such cases reacted well to brisk purgation and enemata with a predominantly farinaceous and milk diet: calomel was excellent for the former, and it could with advantage be administered with a capsule of naphthol. Personally he had great faith also in capsules containing pure carbolic acid, given between meals if gastric fermentation co-existed. He referred to an important class—what he would call a diathetic class—of the insanities which the text-books as yet had not recognized. He did not refer to the so-called gouty or rheumatismal insanities, but to those associated with and growing in the soil of myxœdema and acromegaly, with a very constant and distinct physiognomy of their own, and with a pathogenesis that could be harmonized and well explained by the morbid changes present, changes which lay at the root of the mental as well as the bodily conditions. In the one case (myxœdema), a morbid process starting from the thyroid gland affected the whole capacity of the blood in regard to its power of taking up oxygen from the air. On examining the blood with the mercurial pump it was found that its gases O and CO_2 were much diminished, and by placing the individual in the apparatus for examining the gases of respiration, it was found out that he took in but little oxygen and correspondingly gave out but little CO_2 during life. Thus he suffered from weakness and dullness, from subnormal temperature, and from a tendency to the accumulation of incompletely oxidized bodies (fat, etc.) in his tissues. Similarly in the insanity of acromegaly pituitary feeding gave corresponding benefit, and for those who cared to follow the function of this gland and its special relation to the brain and nervous system he would refer to his paper on the pituitary, published in the *British Medical Journal*, January, 1894. Finally,

as to toxins formed in the central nervous organs, this possibility must not be overlooked. Toxins may form in muscle and gland from the chemical products generated during the activity of such tissues—*e. g.*, CO_2 , lactic acid, creatine, etc. Now, in the central nervous system there was a very complex lymph apparatus for the absorption, carrying off, and elimination of these metabolic waste products. The whole nervous tissue of brain and spinal cord and the sheaths of the cranial and spinal nerves were perforated by a system of lymph channels, which in the brain cortex itself formed a special prolongation around each of the larger nerve cells (pericellular lymph sacs), and which had peculiar relationships with the adventitial sheaths of the pia-arachnoid and intracerebral blood-vessels. In the general paralytic and in the chronic alcoholic these lymphatic structures were affected in a special and peculiar way, producing in places blockages of the lymph streams and overgrowth of these lymphatic (lymph-secreting and lymph-absorbing) cells, which, according to their local incidence and preponderance, affected different spots, centres, and tracts of the central nervous system. An associated paresis of the muscular coats of the blood-vessels followed by fusiform and ampullary dilatations of the vascular and lymphatic channels also coexisted and added to the complexity of the morbid involvement, and this apart from changes which took place in the dynamic connections of nerve cells (dynamic changes) and in the internal nutrition of the cells, bodies and protoplasm (nutritive changes). The products of metabolism of the nerve cells would thus be in places retained in the dilated or obstructed sacs and lymphatic channels, producing from time to time—*i. e.*, continuously or cumulatively—various symptoms of toxism; the toxin being in such cases the unescaped, uneliminated products of cell activity. He concluded by stating that more often than not toxic agencies played a part in the *course of an insanity which was already established*; in a small number they played a *truly causal* part, but that in any case they

should be vigorously treated when indications of their presence existed, the treatment being lavage or enemata, purgation with calomel, and antiseptic drugs taken internally; while to aid the convalescent stage and its associated anæmia iron, extract of bone marrow, etc., were indicated.

Dr. HARE said that, in listening to the paper, he had been struck by the fact of the large amount of knowledge the ancients possessed on the subject-matter discussed by the author. The central point insisted upon was that of self-poisoning in relation to mental conditions; in other words, the connection between such states of the mind and of the nervous system and the processes of disintegration and disease within the body. But the physicians of two thousand years ago were well acquainted with these facts, and they used such terms as "melancholia" and "hypochondriasis," "black bile," and "under the cartilages," showing that the Greeks well knew the relation between mental disturbances and affections of the liver. But the physicians of the present day had demonstrated what was previously only known as the result of clinical observation. There was nothing of which he was more sure than this self-poisoning, not only in insanity, but in many other conditions; and doubtless they would sadly neglect the treatment of many cases of insanity if they did not pay attention to the condition of the digestive organs. He was glad to hear the author insist upon the value of calomel and purgatives.

Dr. THEODORE WILLIAMS observed that in this country one ought not to suffer so much from mental and other diseases due to defective excretion, because great attention was usually paid to regularity of bowels and the proper function of the skin. On this ground, if the author's hypotheses were correct, such mental disturbances ought to be much more common in countries where it was quite common for persons to have an action of the bowels only once a week, and then only from purgation, and it was well known that the skin was not so well looked after there as here.

Dr. BOWER suggested that probably the intestinal trouble was more often the result of the nervous trouble than the cause. In respect of alcoholic insanity, it was said that the neuroses made the patient drink, and the drink reacted on the neuroses. He thought that washing out the stomach and intestines was of the greatest possible advantage.

Dr. FORBES WINSLOW observed that the subject was a very difficult one unless one had practical experience in a large institution. Patients in private practice did not afford sufficient opportunities to justify them in coming to any conclusion on the subject. As, however, the question was being raised in the House of Commons as to the increase in the prevalence of insanity and its causes, it was a great thing to have a paper like the one to which they had just listened. The mention of the influence of uric acid in the system reminded him of a case of a man suffering from gout who had melancholia with monomania. After a time the presence of a stone in the bladder was made out, and on its removal all his delusions disappeared.

Dr. HAMILTON, in replying, thanked the president for his kind words of welcome and wished to say that his paper was simply suggestive of the vast possibilities of the subject. He had recognized the conditions so clearly enumerated by Sir Crichton Browne, which all played an important part in the causation of mental disease, and he proposed at a future time to publish further details of his investigations. The speaker was disposed to regard the conclusion of Dr. Haig, whose views of gout are so well known, as extreme in the present instance, and while he recognized the fact that increased uric-acid excretion was found in many nervous disorders, he regarded these phenomena as the result of intestinal derangement such as he, the speaker, had demonstrated, rather than the initial cause, and he referred to Dr. Haig's own writings in regard to the transferral of cerebral and joint symptoms as an illustration. While he recognized the importance of the study of insanities associated with

myxœdema and acromegaly, and the formation of certain alkaloids in the nervous system, he did not feel that the scope of the paper permitted him to go into this question, which seemed to have been so diligently studied by Dr. Andriezen. As to the query of his friend, Dr. Theodore Williams, regarding the antipathy of the French to water and to the carelessness regarding the ordinary functions of Nature and their relation with Gallic insanity as compared with the better habits of their Anglo-Saxon neighbors, he had his own views. In conclusion, while disclaiming any dogmatism, he still would insist that in most cases of suddenly developing acute mania, and especially such forms as the puerperal and periodic varieties, the existence of intestinal autotoxis could be very often found.

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